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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/552,206

09/14/2006

Irina Velikyan

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11/03/2010

GE HEALTHCARE, INC.

IP DEPARTMENT 101 CARNEGIE CENTER

PRINCETON, NJ 08540-6231

EXAMINER

PERREIRA, MELISSA JEAN

ART UNIT

PAPER NUMBER

1618

MAIL DATE

DELIVERY MODE

11/03/2010

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.



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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Application Number: 10/552,206
Filing Date: September 14, 2006
Appellant(s): VELIKYAN ET AL.

Craig M. Bohlken
Reg. No. 52,628
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 8/23/10 appealing from the Office action mailed 3/23/10.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application:

Claims 1-19

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the

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subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

(8) Evidence Relied Upon

5,439,863	Bottcher et al.	8-1995
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WO03/059397A2	Griffiths et al.
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GB2056471A	Maier-Borst et al.
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Wheaton, R.M. "Properties of Strongly Basic Anion Exchange Resins" Industrial and Engineering Chemistry, 1951, 43, pp. 1088-1093

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Griffiths et al. (WO03/059397A2) in view of Bottcher et al. (US 5,439,863) and further in view of Maier-Borst et al. (GB 2056471A) and Wheaton et al. (*Industrial and Engineering Chemistry* **1951**, 43, 1088-1093).

Griffiths et al. (WO03/059397A2) discloses the method of producing a ^{68}Ga -radiolabeled complex/ ^{68}Ga -labeled targeting agent for use in PET detection (p4, paragraph 2; p9, paragraph 1). The method of obtaining the ^{68}Ga involves eluting ^{68}Ga from a $^{68}\text{Ge}/^{68}\text{Ga}$ titanium dioxide based in-house generator. The ^{68}Ga is eluted from the titanium dioxide generator, which can be fitted with an anion-exchange membrane/Q5F cartridge (p14, paragraph 1) with acidic solution, such as 0.5-1N HCl (p7, paragraph 3; p8, paragraph 2; p12, paragraph 1). The method of producing a radiolabeled gallium complex involves reacting the solution of a peptide labeled macrocyclic chelate with the ^{68}Ga diluted from the $^{68}\text{Ge}/^{68}\text{Ga}$ titanium dioxide generator (p14, paragraph 1). The chelate-targeting agent conjugates can be compounded into kits that are ready to use and accept the ^{68}Ga elute (p8, paragraph 3). The macrocyclic-chelating agent, such as DOTA or NOTA may be linked to a peptide that can target the site of a disease, thus generating a bifunctional chelating agent comprising a targeting vector which will be site-specific (p9, paragraph 1; p11, paragraphs 1 and 2). Griffiths et al. does not disclose the preparation of the chelate-targeting agent conjugates via microwave acceleration. Griffiths et al. also does not disclose an anion exchanger comprising HCO_3^- or more specifically one comprising an amine functional groups or one based on polystyrene-divinylbenzene.

Bottcher et al. (US 5,439,863) discloses the preparation of metal complex salts via microwave irradiation (column 3, line 44-46). The complexes are prepared from metal ions, such as those of the second and third main group, not excluding gallium and multitoothed chelating ligands that occupy more than one coordination site on the

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central metal atom (column 3, lines 55-59; column 4, lines 44-46). The ligands of the disclosure may include those with dioxime (N and O containing), etc. groups (column 5, lines 20-24). The use of microwave as the high-energy input allows for a continuous conversion, single-stage reaction with short reaction time and ease of separation of the formed complexes (column 4, line 19; column 5, lines 66+; column 6, lines 1-5).

Maier-Borst et al. (GB 2056471A) discloses the separation of ^{68}Ga for its parent nuclide, germanium-68, with 5N HCl and water via passing the eluant from a generator column into an anion exchanger comprising quaternary ammonium groups incorporated in a matrix of styrene and divinylbenzene and washing the anion exchanger with water (p4, lines 44-48).

Wheaton et al. (*Industrial and Engineering Chemistry* **1951**, 43, 1088-1093) discloses strongly basic anion exchange resins which are quaternary ammonium salts having a polystyrene crosslinked with divinylbenzene base (Dowex 1 and 2) (p1088, paragraph 1). Dowex 1 and 2 are provided in various ionic forms, such as bicarbonate (table I; table II).

At the time of the invention it would have been obvious to produce a ^{68}Ga -DOTA-peptide complex for use as a PET tracer via the production of ^{68}Ga from a $^{68}\text{Ge}/^{68}\text{Ga}$ titanium dioxide generator as disclosed by Griffiths et al. The microwave synthesis technique for the method of producing metal-chelate complexes was known by Bottcher et al. thus, it would have been obvious to utilize the microwave acceleration technique for a faster, more reproducible preparation of the ^{68}Ga -DOTA-peptide complex, such as that of Griffiths et al. to generate a complex useful in the treatment or diagnosis of

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tumours with minimal side product formation. Microwave acceleration techniques have been utilized since the 1980's in a number of production methods for radioactive precursors and radiotracers labeled with positron-emitting nuclides. The microwave method is mostly associated with shortened reaction times and encompasses the microwave conditions of the instant claims. Since the microwave technique was known in the art (Bottcher et al.) one would have a reasonable expectation of success for preparing radiotracer via labeling reactions with this improved microwave technique.

It is known in the prior art to add a chelating agent, such as EDTA to elute ^{68}Ga from an aluminum oxide exchanger. The disadvantage of forming the ^{68}Ga -EDTA complex is that the complex has to be destroyed before further processing to obtain radiopharmaceutical agents which is time-consuming and expensive (see Maier-Borst et al. p1, lines 10-16). It would have been obvious to one ordinarily skilled in the art to utilize the anion exchanger of Maier-Borst et al. to separate ^{68}Ga from its parent nuclide since no chelating agent is required for separation, as Maier-Borst et al. is drawn to the same method of the separation of ^{68}Ga from ^{68}Ge without the use of an EDTA chelating agent. Thus, it would have been predictable and favorable to utilize the anion exchanger of Maier-Borst et al. to avoid the extra step of destroying a ^{68}Ga -EDTA for further processing to obtain radiopharmaceutical agents.

At the time of the invention it would have been obvious to one ordinarily skilled in the art that the anion exchange resin comprising quaternary ammonium groups incorporated in a matrix of styrene and divinylbenzene may comprise the bicarbonate

counterion as the bicarbonate provides for a minimal amount of swelling and thus greater selectivity of the anion exchange resin (Wheaton et al. p1089, resin swelling).

Claims 1,3-7 and 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Maier-Borst et al. (GB 2056471A) in view of Wheaton et al. (*Industrial and Engineering Chemistry* **1951**, 43, 1088-1093).

Maier-Borst et al. (GB 2056471A) discloses the method of obtaining ^{68}Ga by the separation of ^{68}Ga for its parent nuclide, germanium-68, with 5N, 0.5N HCl and water via passing the eluant from a series of a generator column (in HCl) into an anion exchanger comprising quaternary ammonium groups incorporated in a matrix of styrene (in H_2O) and divinylbenzene and washing the anion exchanger with water (example 6; p4, lines 44-48). Maier-Borst et al. does not disclose the anion exchanger comprising HCO_3^- as counterions.

Wheaton et al. (*Industrial and Engineering Chemistry* **1951**, 43, 1088-1093) discloses strongly basic anion exchange resins which are quaternary ammonium salts having a polystyrene crosslinked with divinylbenzene base (Dowex 1 and 2) (p1088, paragraph 1). Dowex 1 and 2 are provided in various ionic forms, such as bicarbonate (table I; table II).

At the time of the invention it would have been obvious to one ordinarily skilled in the art that the anion exchange resin comprising quaternary ammonium groups incorporated in a matrix of styrene and divinylbenzene may comprise the bicarbonate

counterion as the bicarbonate provides for a minimal amount of swelling and thus greater selectivity of the anion exchange resin (Wheaton et al. p1089, resin swelling).

(10) Response to Argument

Appellant asserts that Griffiths et al. is silent on anion exchangers using HCO_3^- or containing amine functional groups or based on polystyrene-divinylbenzene.

The reference of Griffiths et al. was not used to teach of anion exchangers using HCO_3^- or containing amine functional groups or based on polystyrene-divinylbenzene. The reference of Griffiths et al. was used to teach of the method of obtaining ^{68}Ga that involves eluting ^{68}Ga from a $^{68}\text{Ge}/^{68}\text{Ga}$ titanium dioxide based in-house generator. The ^{68}Ga is eluted from the titanium dioxide generator, which can be fitted with an anion-exchange membrane/Q5F cartridge, with acidic solution (e.g. 0.5-1N HCl). The eluted ^{68}Ga is used for the method of producing a ^{68}Ga -radiolabeled complex/ ^{68}Ga -labeled targeting agent for use in PET detection.

The reference of Maier-Borst et al. was used to teach of the separation of ^{68}Ga for its parent nuclide, germanium-68, with 5N HCl and water via passing the eluant from a generator column into an anion exchanger comprising quaternary ammonium groups incorporated in a matrix of styrene and divinylbenzene and washing the anion exchanger with water.

It is known in the prior art to add a chelating agent, such as EDTA to elute ^{68}Ga from an aluminum oxide exchanger. The disadvantage of forming the ^{68}Ga -EDTA complex is that the complex has to be destroyed before further processing to obtain radiopharmaceutical agents which is time-consuming and expensive (see Maier-Borst et

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al. p1, lines 10-16). It would have been obvious to one ordinarily skilled in the art to utilize the anion exchanger of Maier-Borst et al. to separate ^{68}Ga from its parent nuclide since no chelating agent is required for separation, as Maier-Borst et al. is drawn to the same method of the separation of ^{68}Ga from ^{68}Ge without the use of an EDTA chelating agent. Thus, it would have been predictable and favorable to utilize the anion exchanger of Maier-Borst et al. to avoid the extra step of destroying a ^{68}Ga -EDTA for further processing to obtain radiopharmaceutical agents.

Appellant asserts that the prior art (Maier-Borst et al.) ^{68}Ga generator referred to there uses an aluminum oxide column. Present claim 2 has a titanium dioxide column as an essential feature. That is completely different to aluminum oxide.

The reference of Maier-Borst et al. was not used to teach of a titanium oxide generator column but was used to teach of contacting the eluant from a $^{68}\text{Ge}/^{68}\text{Ga}$ generator column with an anion exchanger comprising quaternary ammonium groups incorporated in a matrix of styrene and divinylbenzene and subsequent washing of the anion exchanger with water. The anion exchanger of the disclosure encompasses the anion exchanger of the instant claims and therefore is capable of the same functions, such as binding ^{68}Ga and has the same properties. Further, the wash water of the disclosure is capable of eluting the bound ^{68}Ga from the anion exchanger as evidenced by the specification p9, example 1.

The reference of Griffiths et al. was used to teach of the method of obtaining the ^{68}Ga via a $^{68}\text{Ge}/^{68}\text{Ga}$ titanium dioxide based in-house generator which may be optionally fitted with an anion-exchange membrane as well as that stated above. The eluted ^{68}Ga

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is used for the method of producing a ^{68}Ga -radiolabeled complex/ ^{68}Ga -labeled targeting agent for use in PET detection.

Therefore, at the time of the invention it would have been obvious to one skilled in the art to contact the elute from a $^{68}\text{Ge}/^{68}\text{Ga}$ generator column, such as titanium dioxide of Griffiths et al. with an anion exchanger, such as that of Maier-Borst et al. to separate ^{68}Ga from its parent nuclide, ^{68}Ge since no chelating agent is required for separation, as Maier-Borst et al. is drawn to the same method of the separation of ^{68}Ga from ^{68}Ge without the use of an EDTA chelating agent. Thus, it would have been predictable and favorable to utilize the anion exchanger of Maier-Borst et al. to avoid the extra step of destroying a ^{68}Ga -EDTA for further processing to obtain radiopharmaceutical agents, such as the ^{68}Ga -radiolabeled complex/ ^{68}Ga -labeled targeting agent for use in PET detection of Griffiths et al.

Appellant asserts that Wheaton et al. teaches that there are 5 resins (iodide, bromide, nitrate, nitrite and chloride) that would all have superior characteristics to bicarbonate with regards to the minimizing the swelling characteristics of the resin as Wheaton et al. teaches that bicarbonate provides for a "...minimal amount of swelling and thus greater selectivity..." Appellant contend that the person skilled in the art, if *arguendo* assumed to be seeking to modify Maier-Borst et al. based on resin selectivity as taught by Wheaton et al., would choose one or more of iodide, bromide, nitrate, nitrite or chloride ahead of bicarbonate.

Wheaton et al. teaches that the bicarbonate form of the Dowex 2 is shown to have increased stability for several days, even at higher temperatures (e.g. 95°C) and

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minimal swelling (4%) wherein the anion form of the Dowex with the maximum swelling is 13%. The bicarbonate form of the Dowex 2 is one of a finite number of anionic forms of the Dowex 2 wherein the less preferred embodiment (bicarbonate) is similar and/or equivalent to the preferred embodiment/standard (chloride) as Wheaton et al. states that the volume changes of Dowex 2 in different salt concentrations and in different ionic forms are not large, which is an added advantage of this resin (Wheaton et al. p1089, Resin Swelling). Thus, the reference of Wheaton et al. does not teach away from the use of the bicarbonate form of the Dowex 2.

In response to appellant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Michael G. Hartley/

Supervisory Patent Examiner, Art Unit 1618

Conferees:

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